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CHAPTER VII

TREATMENT OF TOBACCO DEPENDENCE

CONTENTS

Introduction	465
Treatment.....	470
Nicotine Replacement Strategies	470
Forms of Replacement and Rationale	471
Nicotine Polacrilex Gum.....	471
Withdrawal Symptom Relief	472
Cravings-Urges-Desires	475
Efficacy Trials.....	475
Dose and Patient Relationship	478
Nasal Nicotine Solution.....	479
Nicotine Transdermal Patch.....	479
Nicotine Aerosols.....	480
Comparisons of Preparations.....	480
Dependence on Nicotine Replacement.....	481
Other Pharmacologic Approaches	481
Nonspecific Pharmacotherapy-Symptomatic	
Treatment.....	481
Treatment of Discomfort Associated With	
Tobacco Withdrawal.....	482
Treatment of Abstinence-Associated Mood	
Changes	483
Nicotine Blockade Therapy.....	484
Deterrent Therapy	485
Conclusions.....	486
Behavioral Treatment Strategies	487
Aversion Procedures	488
Satiation	488
Rapid Smoking.....	491
Reduced-Aversion Techniques.....	492
Relaxation Training	493
Contingency Contracting	494
Social Support.....	495
Coping Skills Training.....	496
Stimulus Control.....	497
Nicotine Fading.....	497
Controlled Smoking.....	499
Multicomponent Programs.....	500
Other Treatment Strategies.....	504

Hypnosis	504
Acupuncture	504
Treatment of Special Smoker Populations.....	505
Applying Smoking Interventions to Women...	505
Sex Differences in Cessation and Relapse	
Rates.....	505
Motivation to Quit.....	506
Education.....	506
Social Values and Beliefs.....	507
Achieving Abstinence.....	507
Weight Gain.....	507
Stress Management.....	508
Social Support.....	508
Smoking Cessation Initiatives for Black	
Americans.....	508
Sociodemographic Factors.....	509
Restricted Health Care Access.....	509
Social Norms and Advertising Influences...	509
Determinants of Quitting Motivation and	
Success Among Black Smokers.....	510
Smoking and Quitting Patterns Among	
Black Americans.....	510
Quit-Smoking Treatments.....	511
Quitting Methods.....	511
Sources/Treatment Agents.....	511
Messages/Methods.....	511
Channels/Delivery Modes.....	511
Interventions for Smoking Cessation Among	
Hispanics.....	512
Prevalence.....	512
Smoking Antecedents.....	512
Smoking Interventions.....	513
Methodological Issues in Treatment Study Design	
and Evaluation.....	513
Conclusions.....	516
<hr/>	
Relapse	517
Defining Relapse	518
Conceptual Frameworks.....	518
Predisposing Factors	520
Demographics.....	520
Smoking and Quitting History	521
Smoking History	521
Smoking Typologies.....	521
Quitting History.....	522
Withdrawal and Dependence.....	522

Cognitive Factors.....	523
Concern About Weight Gain.....	523
Self-Efficacy.....	524
Outcome Attributions.....	525
Social Factors.....	526
Smoking Cues.....	526
Social Support.....	526
Global Support.....	527
Smoking-Specific Support.....	527
Stress.....	528
Precipitating Factors.....	529
High-Risk Situations.....	529
Coping Strategies.....	530
Abstinence Violation Effect.....	532
<hr/>	
Summary and Conclusions.....	532
<hr/>	
References.....	534

Introduction

The previous chapters have established that nicotine is a drug of dependence. Chapter II provided a detailed description of the pharmacokinetics and pharmacodynamics of nicotine from various forms of tobacco. Chapter III addressed sites and mechanisms of nicotine action. Chapter IV documented addictive properties of tobacco including those related to its use as a vehicle for nicotine delivery and physiological dependence produced by nicotine administration. Chapter V demonstrated the commonalities between tobacco use and use of other drugs such as heroin and cocaine. Chapter VI discussed effects of nicotine that may promote tobacco use.

Unfortunately, much of this work has seen limited clinical application in the treatment of the tobacco user. Most current treatment approaches are primarily psychological. Relatively few studies have addressed pharmacologic determinants of tobacco use (Pomerleau et al.). An increased understanding of the addictive properties of nicotine should lead to improved treatment approaches. Interventions for tobacco users who seek assistance should consider the addictive properties of tobacco and the ways that these can be overcome. They should also be sensitive to other effects of nicotine that may promote tobacco use. The failure to address these types of issues may be an important cause of the less than optimal results attained by existing treatment approaches.

It is evident that smoking is maintained by both pharmacologic and psychological determinants. The relative contributions of these factors are virtually impossible to separate and are likely to vary dramatically not only among individual smokers, but perhaps also within individuals at different times and stages of their smoking histories. Pharmacologic and psychological factors become closely linked in a conditioning process in which smoking is associated with multiple cues. A typical smoker who has averaged 20 cigarettes/day over a 15-year period is likely to have taken more than 1 million puffs during the course of his or her smoking history. The highly dependent smoker who presents for treatment tends to have an even longer and more extensive history of nicotine self-administration than does the average smoker. The sheer magnitude of this overlearning appears unmatched in any other form of drug abuse.

Cues associated with smoking (an ashtray, the sight of another person smoking) can elicit strong cravings not only in current and newly abstinent smokers, but also in individuals who have achieved longer term abstinence (Abrams 1986). Some cues may extinguish relatively quickly upon cessation. Others may be more problematic, especially in long-term dependent smokers (Abrams et al., in press). Smokers who report smoking more when they are angry, frustrated, or unhappy may be especially vulnerable to a crisis even when the crisis occurs after an extended period of abstinence (Pomerleau,

Adkins, Pertschuk 1978). Cues associated with smoking that are encountered only infrequently might continue to elicit conditioned cravings over a longer time period (Abrams et al., in press).

Individual differences should also be considered. Conditioning histories vary among smokers, although there are also likely to be important commonalities. Some smokers have relied more heavily upon nicotine in regulating mood, especially negative affect (Chapter VI). Others have used cigarettes as a means of sustaining attention to monotonous tasks. Still others have used cigarettes more frequently as an aid to relaxation (Ikard, Green, Horn 1969; Chapter VI). Few experimental studies have related individual differences to reasons for smoking (Ikard and Tompkins 1973; Leventhal and Avis 1976).

Physiological reactions (e.g., elevated heart rate) to smoking cues have been documented to persist for extended intervals (Abrams et al., in press). The interaction of physiological, social, conditioning, and cognitive factors may be critical. The combination of tobacco pharmacology and users' conditioning histories can help to explain cravings even after long periods of abstinence. Expectations concerning the consequences of tobacco use also appear to be extremely important. Thus, among individuals who are currently abstinent, the anticipation of highly reinforcing physiological reactions to tobacco use is predictive of relapse (Marlatt and Gordon 1985).

It is ironic in light of the broad-spectrum treatment of other drug dependencies that tobacco prevention and cessation treatments have been focused so narrowly. Even where pharmacologic strategies have been employed (e.g., nicotine replacement therapy; Fagerström 1982b; Schneider et al. 1983), these often have not been integrated systematically with behavioral treatments. Chapter V details some of the physiological and psychosocial interventions for various drug dependencies including those on alcohol, opiates, cocaine, and other illicit substances. This body of literature may have important and largely overlooked implications for the clinical treatment of tobacco dependence.

According to the 1985 National Health Interview Survey (NHIS), there are approximately 41 million former smokers in the United States. Approximately 90 percent of former smokers report that they quit smoking without formal treatment programs or smoking cessation devices (Fiore et al., in press). Achieving abstinence from tobacco and other substances outside the context of formal treatment programs (spontaneous remission) is discussed in Chapter V. Not only smokers but other drug takers often discontinue use of the dependence-producing substance outside the context of formal intervention. Several common factors may be operating to influence smokers to quit (e.g., response to social pressures, observed and anticipated health consequences). Unfortunately, millions of new individuals have been recruited to smoking.

Despite the well-known health hazards of smoking and the documented difficulties in quitting, few intensive treatment options are available to the highly dependent smoker (Sachs 1986). Cigarette dependence or addiction can be as intractable as any addictive disorder (Russell 1976). Studies have found considerable similarity in relapse processes between tobacco and other drugs of dependence (Hall and Havassy 1986; Marlatt and Gordon 1980; see also Chapter V).

As shown in Chapter IV, cigarette smoking is not a random or capricious behavior; rather it is orderly and controlled. The role of nicotine in cigarette smoking is functionally similar to the roles of other addicting, psychoactive drugs in behaviors that lead to their self-administration (Chapter V; US DHHS 1984b, 1987).

A practical result of these conclusions has been the development of methods to treat cigarette smoking that are similar to methods used to treat other forms of drug dependence. An additional implication is that because cigarette smoking, like other forms of drug dependence, involves both pharmacologic and behavioral factors, treatment approaches also may involve pharmacologic agents, behavioral strategies, or a combination of these. There is some evidence, as discussed in the present Chapter, that treatment approaches which address both pharmacologic and behavioral factors are most effective.

Current data indicate that smoking prevalence is declining much more rapidly among certain segments of the population (e.g., better educated, higher income, professional) than among others (blue collar, minority, less educated, lower income) (Appendix A). Individuals from lower socioeconomic status (SES) backgrounds appear to have less access to treatment and may be less likely to enroll in treatment programs when they are available. Participants in most formal treatment programs have been from the middle and upper-middle class (US DHHS 1987). To have maximum impact upon the prevalence of smoking, interventions must be responsive to and meet the needs of lower SES smokers in a variety of circumstances.

Women represent an additional population that could benefit from tailored programming. Women may be more likely to use cigarettes for stress reduction and mood regulation (Brunswick and Messeri 1984; Mitic, McGuire, Neumann 1985). Potential weight gain may represent an especially serious concern for many female smokers (Jacobson 1981; US DHEW 1980; Chapter VI).

Knowledge of the dependence-producing aspects of tobacco underscores the need for early intervention in preventing habitual chronic tobacco use. This approach needs to be sensitive to both pharmacologic and social aspects of smoking. Intervention for children and adolescents also may need to focus upon cessation of well-established smoking patterns in addition to the prevention of smoking onset.

Treatments that assist smokers to achieve initial cessation and to maintain long-term abstinence are needed. High rates of relapse plague the vast majority of treatment programs as well as self-initiated quit attempts. Close examination of the physiological, psychological, and social factors that promote relapse should suggest more effective intervention strategies. Conceptualizing the quitting process as ongoing may also be useful (Marlatt and Gordon 1985; Prochaska and DiClemente 1983). Work is needed not only to reduce the risk of initial relapse, but to accelerate recycling of quitting attempts in the event that relapse does occur (Glasgow, Lando, Rand 1986).

Although discussed in earlier chapters in this Volume, it is appropriate to summarize some observations about cigarette smoking that are important in the development and implementation of treatment strategies.

1. Chronic tobacco use produces physical dependence such that cessation may be accompanied by a withdrawal syndrome that includes feelings of discomfort or distress, reduced capacity to work or handle stressful situations, and heightened urges to resume smoking.
2. Consumption of tobacco products, which inevitably results in administration of nicotine, can produce effects which are perceived as desirable or otherwise useful to the cigarette smoker, thereby providing a strong incentive for cigarette smoking. There is evidence that nicotine can enhance performance of smokers on certain types of attention and memory tasks. Nicotine also exerts an important role in the relationship between smoking and body weight.
3. The desire to handle cigarettes may be an important reason for smoking (Leventhal and Avis 1976). Such stereotypical behaviors are characteristic of other forms of drug addiction and other compulsive behaviors not involving psychoactive drug self-administration. For cigarette smoking, the behaviors appear to occupy small periods of time with hand-oral manipulations (Ikard, Green, Horn 1969).
4. Nicotine may reduce the aversiveness of stressors for smokers (Pomerleau, Turk, Fertig 1984). Stress has been demonstrated to increase the rate of smoking (Leventhal and Cleary 1980; Schachter, Silverstein, Perlick 1977; Chapter VI).
5. There are numerous environmental factors that can facilitate the initiation and maintenance of smoking (e.g., peer pressure, family influences, images conveyed in tobacco advertising, association with social and work activities) (Flay 1985b; Warner 1986).

Smoking treatment programs are designed to counter these important motivations to smoke. For example, skills training

treatments are designed to inculcate skills so that individuals can cope with stressors or negative affective states without smoking. Aversion treatments are designed to condition cigarette aversions so that smokers anticipate little pleasure from smoking. Nicotine polacrilex gum and nicotine fading treatments are designed to reduce the magnitude of the nicotine withdrawal syndrome. This Chapter attempts to summarize what is known about how pharmacologic and behavioral treatments exert their clinical effectiveness. Knowledge of how treatments influence smoking will be the base on which more effective treatments are designed.

This Chapter describes pharmacologic, behavioral, and combined treatments applied in clinical and laboratory settings. It concentrates on work published since the last major Surgeon General's review of smoking treatment (US DHEW 1979), but refers back to that Report for historical perspective. Pharmacologic and behavioral treatment strategies are reviewed in light of the current acceptance of tobacco use as a form of drug self-administration that has clear addictive properties as well as commonalities with other forms of drug abuse.

The review of treatment approaches is necessarily selective. Smoking interventions can be placed along a clinical-public health continuum. At the extreme clinical end are intensive and costly one-to-one interventions, often with a highly trained provider. Examples include one-to-one behavioral or psychological counseling. Proceeding somewhat toward the public health end, one finds group programs, many of them offered by nonprofit or voluntary organizations, but some also conducted on a proprietary basis. These programs typically entail 4 to 10 sessions and are usually led by facilitators with some background in health education and psychology, although trained lay facilitators are also used. Further along the public health segment of the continuum are minimal interventions emphasizing self-help manuals and including brief contact with physicians during office visits.

The current Chapter focuses primarily upon the treatment of smokers who seek assistance in quitting. There is no intent, however, to deny the importance of public health interventions that will ultimately reach a far greater number of smokers. Both clinical and public health approaches are absolutely essential. The reader is referred to previous Surgeon General's Reports and other publications for more detailed discussions of such topics as physician intervention, self-help strategies and outcomes, workplace and community interventions (US DHEW 1979; US DHHS 1982, 1984b, 1985; Schwartz 1987).

Treatment

Although most pharmacologic treatment strategies also encompass behavioral components and some studies have systematically combined pharmacologic and behavioral interventions, it is conceptually useful to consider these two major types of approaches separately.

One major pharmacologic approach has involved various nicotine replacement strategies. As discussed in Chapter V, the general principle of replacement therapies for drug dependence is to present the patient with a safer and more therapeutically manageable form of the drug that directly alleviates signs and symptoms of withdrawal and craving (Jaffe 1985). These strategies are modeled after those originally developed to treat dependence on heroin and other opiates (Henningfield and Jasinski 1988). A variety of nontobacco-based delivery systems provide potentially effective means for nicotine replacement. Experimental and theoretical aspects of each of these delivery systems have been described in part in Chapter IV. In the present Chapter, data regarding those nicotine delivery systems that are most relevant to direct treatment application will be summarized.

In addition to nicotine replacement approaches, the following additional pharmacologic treatment approaches developed for other forms of drug dependence may be applied to tobacco dependence: Nonspecific Pharmacotherapy, in which the patient is treated symptomatically; Nicotine Blockade Therapy, in which the behavior-controlling effects of the dependence-producing drug are blocked by pretreatment with an antagonist; and Deterrent Therapy, in which administration of the treatment drug results in the occurrence of aversive consequences. All three approaches have potential applications in the treatment of cigarette smoking. Each of these strategies is discussed.

Nicotine Replacement Strategies

To date, only one form of nicotine replacement has been approved by the Food and Drug Administration (FDA): nicotine polacrilex chewing gum (2-mg pieces only). Three other nicotine delivery systems that will be briefly discussed are (1) a transdermal patch for delivery of nicotine through the skin, (2) a nasal nicotine solution, and (3) a nicotine vapor inhaler (smokeless cigarette).

There is considerable current interest in nicotine replacement strategies for smoking cessation because (1) nicotine is the critical dependence-producing component in tobacco, (2) some treatment outcome data on the efficacy of the first nicotine replacement procedure to be evaluated (nicotine polacrilex gum) are encouraging, and (3) other forms of nicotine substitution may hold further

potential for more effective treatment. The assumption underlying this treatment approach is that nicotine-specific withdrawal interferes with successful cessation and can be prevented or attenuated by nicotine replacement, thereby both promoting cessation and aiding the inhibition of relapse. For a more extensive review of nicotine replacement, see Grabowski and Hall (1985) and Pomerleau and associates (1988).

Forms of Replacement and Rationale

The first reported systematic use of nicotine replacement to help people quit smoking was the intravenous administration of nicotine by Johnston (1942). This approach is not clinically practical because of the short half-life of nicotine (Chapter II) and its potential toxicity with excessively rapid administration (Appendix B). The next systematic approach was the development of nicotine polacrilex gum by Ferno, Lichtneckert, and Lundgren (1973). The weaning from nicotine would actually begin with the switch from cigarettes to gum in that nicotine polacrilex (1) produces slower-rising plasma nicotine levels than cigarettes and (2) reduces the inhaled nicotine bolus effect believed to contribute to nicotine's addictive potential in smoke (Russell and Feyerabend 1978; Chapter II).

The same rationale applies to other replacement approaches (Jarvik 1986; Russell 1986) including nicotine transdermal delivery systems, nasal nicotine solution (NNS), and smoke-free nicotine cigarettes. The different forms allow variations in delivery (dose and speed) which may influence effectiveness, relief of withdrawal, patient acceptance, and outcome.

Nicotine Polacrilex Gum

"Nicotine polacrilex" or "nicotine resin complex" (American Hospital Formulary 1987) is also commonly referred to as nicotine gum. It is a nicotine delivery system in which the nicotine is incorporated into an ion exchange resin base which permits release of nicotine in the proper environment (i.e., saliva in the mouth) when appropriate physical pressure (i.e., chewing) is applied. Twenty to thirty minutes of proper chewing can result in the release of approximately 90 percent of the nicotine (Ferno, Lichtneckert, Lundgren 1973), although there are multiple determinants of how much nicotine actually is absorbed. As discussed in Chapter II, 10 to 15 min of chewing results in the release of approximately 50 to 60 percent of the nicotine in a piece of gum. However, considerable variability exists both within and across subjects (Benowitz, Jacob, Savanapridi 1987; Nemeth-Coslett et al. 1987; Pickworth, Herning, Henningfield 1986; Chapter II). Swallowed nicotine is approximately

70 percent detoxified as a result of its first pass through the liver (Benowitz, Jacob, Savanapridi 1987; Chapter II).

Nicotine polacrilex gum does not usually lend itself to full replacement of the nicotine provided by cigarette smoking. Russell, Feyerabend, and Cole (1976) and McNabb, Ebert, and McKusker (1982) reported that 4-mg-nicotine gum produced plasma nicotine levels approximating that of a 1.2-mg-nicotine-yield cigarette. However, Benowitz, Jacob, and Savanapridi (1987) found only about 50 percent replacement of nicotine levels with 4-mg gum. Benowitz, Jacob, and Savanapridi (1987) reported that chewing 10 pieces of 2-mg gum on an hourly schedule resulted in blood levels of nicotine that were one-third of those achieved while smoking. Therefore, ad libitum chewing of the 2-mg nicotine polacrilex gum probably results in even lower nicotine levels. When nicotine polacrilex gum is chewed, drug levels in plasma rise slowly, peaking in around 20 to 30 min. Although the 4-mg nicotine polacrilex gum replaces nicotine more completely, most testing has proceeded with the 2-mg dose; only the 2-mg dose has been approved for use in the United States. It should be noted, however, that effective nicotine replacement strategies may not require the same range of nicotine blood levels as those produced by cigarette smoking. Even the 2-mg-dose nicotine polacrilex gum has increased smoking cessation rates significantly in several placebo-controlled studies (Table 1).

Withdrawal symptom relief. Several short-term trials (8 hr to 5 days) have found that nicotine polacrilex gum reduced symptoms of withdrawal in comparison to placebo controls (Hughes et al. 1984; Schneider, Jarvik, Forsythe 1984; West, Jarvis, Russell, Carruthers et al. 1984). Jarvis and associates (1982) reported relief of several symptoms for a 6-week period, with scores averaged over weekly sessions. Expectancy may also play a role in withdrawal symptom relief, as suggested in a study by Gottlieb and others (1987). Interpretation of this study is limited, however, by a brief (2-week) observation period and by the possibility that subjects failed to achieve adequate nicotine plasma levels.

In previous studies, not all symptoms were relieved with replacement nor was there consistency among the studies in which symptoms were relieved (Fagerström 1988; West 1984). Irritability was consistently relieved in all studies, whereas hunger, depression, anxiety, difficulty in concentrating, restlessness, annoyance, hostility, and somatic complaints were reduced in some but not others. The degree to which most symptoms are relieved is directly related to the dose of nicotine that is actually obtained when the polacrilex gum is used (Henningfield and Jasinski 1988). The urge to smoke (craving) is not reliably decreased by nicotine replacement (Henningfield and Jasinski 1988; West and Schneider 1987).

**TABLE 1.—Efficacy trials for nicotine polacrilex gum:
Followup abstinence rates (percentages)**

Study	Number ¹	I. Placebo-controlled studies		Followup	P
		Active gum	Placebo		
Puska et al. (1979)	160	35	28	6 mo	N.S.
Malcolm et al. (1980)	210	23	5	6 mo	$p < 0.05$
Fee and Stewart (1982)	352	13	9	1 yr	N.S.
Fagerström (1982b)	96	49	37	1 yr	N.S.
Jarvis et al. (1982)	116	47	21	1 yr	$p < 0.01$
British Thoracic Society (1983)	802	10	14	1 yr	N.S.
Schneider et al. (1983)	60	30	20	1 yr	N.S.
Hjalmarson (1984)	205	29	16	1 yr	$p < 0.05$
Jamrozik et al. (1984)	200	10	8	6 mo	N.S.
Campbell et al. (1987)	985	3	2	1 yr	N.S.
Hall et al. (1987)	139	44	21	1 yr	$p < 0.01$
Study	Number ¹	II. No-gum control studies		Followup	P
		Nicotine gum	No gum		
Russell et al. (1983)	1,938	9	4	1 yr	$p < 0.01$
Fagerström (1984)	145	25	9	1 yr	$p < 0.05$
Hjalmarson (1985)	2,404	25	18	1 yr	$p < 0.05$
Page et al. (1986)	227	12	9	6 mo	N.S.

TABLE 1.—Continued

Study	III. Nicotine polacrilex gum vs. other active treatment				
	Number ¹	Gum	Comparison	Followup	P
Behavioral counseling and rapid smoking					
Raw et al. (1980)	118	38	14	1 yr	p<0.01
Hall et al. (1985)	78	36	28	1 yr	N.S.
Skills training					
Killen et al. ² (1984)	42	23	30	10 mo	N.S.
Acupuncture					
Clavel et al. ³ (1985)	429	12	8	13 mo	N.S.

¹ Number of subjects based on relevant conditions; may not include all subjects assigned to treatment.

² Also included a combined skills training and nicotine polacrilex gum condition.

³ Included a control condition in which subjects were assigned a cigarette case programmed to lock at variable intervals

SOURCE: Modeled after Fagerström (1988).

The studies noted above used ad libitum administration of the 2-mg gum. This level of replacement may be insufficient to reverse some of the symptoms of nicotine withdrawal. Studies which have shown little difference between the 2-mg dose and placebo are not clearly interpretable unless they have confirmed adequate dosing through biochemical markers (e.g., plasma cotinine). When the nicotine polacrilex dose has been increased to 4 mg, more complete reversal of withdrawal (Henningfield, Sampson, Nemeth-Coslett 1986), of electroencephalogram (EEG) changes with abstinence (Pickworth, Herning, Henningfield 1986), and of performance deficits during cessation (Snyder, Davis, Henningfield 1985) is observed.

Different withdrawal symptoms may also require different levels of nicotine replacement. Whether a particular withdrawal symptom is nicotine specific cannot be determined until there is systematic testing by dose and speed of delivery of nicotine replacement. In addition, recent studies show that intrasubject and intersubject variability in chewing can affect the amount of nicotine reaching the circulation (Benowitz et al. 1983; Nemeth-Coslett et al. 1985).

There is also some evidence that weight gain, a significant problem in cessation, can be reduced by nicotine replacement (Fagerström 1987). Even low-dose, 2-mg-nicotine gum has been shown to produce significantly less weight gain over a 10-week period compared with a placebo (Stitzer and Gross 1988).

Cravings-urges-desires. Findings regarding urges or craving are complicated by semantic and measurement considerations (Kozlowski and Wilkinson 1987) and by ambiguity as to what constitutes craving (West and Schneider 1987). Definitions of craving have proven elusive. It is often described as an increase in the desire or urge to use a drug. Although the term craving is used in the present context, a more appropriate phrase might be substituted, e.g., "strength of an urge to use a drug" (Chapters IV and V).

In the tobacco abstinence studies cited above, craving generally was not relieved by nicotine replacement. By contrast, significant relief of craving has been reported with 2-mg-nicotine polacrilex gum compared with placebo controls in an outcome trial (Hjalmarson 1984), in a clinical trial with NNS (Jarvis 1986), and with a nicotine patch in an acute placebo-controlled trial (Rose et al. 1985). The discrepancies may be due to how "craving" is assessed. In a study by Schneider and Jarvik (1985), treatment had no effect on "craving" but did significantly affect "urges to smoke" and "missing a cigarette" from the Shiffman-Jarvik (1976) "craving" subscale. Because nicotine seeking is believed to precede most relapse and its relief is a goal of replacement systems, appropriate operational definitions and testing are essential.

Craving should not be viewed simply as a symptom of a negative withdrawal state. Smokers clearly seek desired effects of nicotine in addition to relief from withdrawal (Chapters II and VI). Nicotine polacrilex gum may reduce negative withdrawal symptoms without providing other effects (e.g., a "high") sought by many smokers.

Efficacy trials. Table 1 summarizes efficacy trials that evaluated nicotine polacrilex gum against placebo controls, no-gum controls, or other active treatment. This Table does not include all the studies that combined nicotine polacrilex gum with behavioral interventions.

The early studies of nicotine replacement involved testing of the nicotine regulation hypothesis (e.g., the extent to which cigarette smokers show compensatory changes in their cigarette smoking behavior; Chapter IV). These studies assessed the capacity of nicotine in polacrilex gum to replace nicotine in cigarettes (Brantmark, Ohlin, Westling 1973; Russell et al. 1976; Turner et al. 1977). Several studies have demonstrated that cigarette smoking can be decreased in laboratory subjects by replacement of the nicotine normally obtained by smoking with nicotine delivered by gum (Nemeth-Coslett and Henningfield 1986). Early clinical outcome